REMARKS

Claims 1-11 are pending and under examination. All of the pending claims stand rejected. The Examiner has also brought several Specification informalities to the Applicants' attention.

In this communication, the Applicants have amended claims 1, 3, 5, and 10 in order to better define certain embodiments of their invention, to further their business interests, and to advance the prosecution of the present application in a manner consistent with the Patent Business Goals (PBG).[1] The present amendments have not been made in acquiescence to the Examiner's arguments and the Applicants specifically reserve the right to prosecute the original (or similar) claims in the future. For similar reasons, Applicants have canceled, without prejudice, claim 4.

In pertinent part, claim 1 has been amended to clarify that the claimed method for detecting target sequences comprises a "detecting step." Support for this amendment can be found throughout the Specification and the claims as originally filed. (*See e.g.*, Specification *p.* 9, *ll.* 23-29; and originally filed claim 4). Claim 4 has been canceled, without prejudice, in view of the amendment to claim 1.

Claims 5 and 10 have been amended to recite, respectively, the phrase "said first/second regions . . . of said target sequence . . .," as appropriate. Claims 5 and 10 have also been amended to further clarify the use of the term "target sequence." Claim 3 has been amended to further clarify the use of the term "cleavage agent." Support for these amendments can be found among other places in the claims as originally filed.

None of the claim amendments or cancellations made herein add new mater. None of the amendments or cancellations made herein are intended to narrow the scope of the Claim within the meaning of *Festo* or related cases.

The rejections at issue are as follows:

1. The Examiner has indicated that the Specification contains various informalities;
2. Claims 1-6 and 10 stand rejected under 35 U.S.C. §112, paragraph 2, as allegedly being indefinite; and

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[1] 65 Fed. Reg. 54603 (September 8, 2000).

2. Claims 1-11 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. 5,994,069 ("'069") to Hall et al.

The Applicants believe that the amendments and remarks presented herein overcome all of the pending rejections/objections thus placing the application in condition for allowance.

1. Specification Informalities

The Examiner has objected to the Specification as containing the following informalities: a) the Verified Statement has not been signed; b) Figures 1A-H, 2A-C, 22A-B, 42A-B, 59A-E, 88A-B, and 99A-E do not have a corresponding description; and c) Figure descriptions 3A-G, 4A-B, and 107 do not have corresponding Figures.

Accompanying this communication is a signed Verified Statement.

Applicants have amended the Specification to address the typographical errors occurring in the descriptions of Figures 1A-H, 2A-C, 22A-B, 42A-B, 59A-E, 88A-B, and 99A-E.

The Applicants have provided revised Figures 3A-G, 4A-B, and 107, attached at Appendix 3, which correct the typographical errors in found in these figures. The revisions are shown in red pursuant to 37 C.F.R. §1.121(d). Upon the Examiner's approval, the Applicants will submit new drawings in compliance with 37 C.F.R. §1.84 that incorporate the proposed changes. Applicants respectfully submit that, as amended, Figures 3A-G, 4A-B, and 107 address and overcome the Examiner's concerns.

2. The Pending Claims Are Sufficiently Definite

Claims 1-6 and 10 stand rejected under 35 U.S.C. §112, paragraph 2, as allegedly being indefinite. (Office Action, *pp.* 2-3). Applicants must respectfully disagree. Applicants respectfully request the Examiner to reconsider the definiteness of the pending claims in view of the above-mentioned amendments to the pending claims.

In particular, the Examiner states that claims 1-6 and 10 are allegedly indefinite "because the preamble [of claim 1] recites a method for detecting a target sequence while the active steps do not recite detecting a target sequence." (Office Action, *p.* 2). As discussed above, the Applicants have amended pending claim 1 to recite the addition of a "detecting

step" (*i.e.*, step "c"). Accordingly, Applicants believe that they have sufficiently addressed the Examiner's concerns and thus overcome this rejection.

The Examiner also states that claims 5 and 10 which are dependent, respectively, upon claims 1 and 7, fail to provide sufficient antecedent basis for the use of the terms "said first/second portion" in reference to the target sequence in view of existing use of the term "first/second regions" when referring to target sequences. (Office Action, *p.* 3). The Applicants have addressed the Examiner's concerns by rewriting the term "said first/second portion" in claims 5 and 10 to recite "said first/second region" as appropriate.

For the reasons stated above, Applicants respectfully submit that the pending indefiniteness rejections should be withdrawn.

3. The Pending Claims Are Not Anticipated By U.S. 5,994,069

The Examiner has rejected claims 1-11 as being anticipated under 35 U.S.C. §102(e) by the '069 patent to Hall et al. The Federal Circuit has held "[a] claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single **prior art reference**." *Verdegaal Brothers v. Union Oil Co., of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); emphasis added). The touchstone of anticipation is the Examiner's citation of a reference that actually qualify as being **prior art** over the claims under examination.

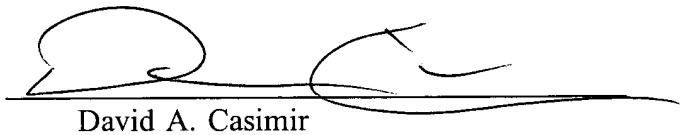
The instant application is a continuation-in-part of U.S. 09/381,212 filed September 17, 1999, which is a 35 U.S.C. §371 application of PCT/US98/05809 filed March 24, 1998, which is a PCT application that claims priority to U.S. 08/823,516 filed March 24, 1997, now issued as **U.S. 5,994,069** on November 30, 1999. Applicants thus respectfully submit that the '069 patent is **not prior art** over the pending application--as the present case claims priority to the '069 patent. Therefore, the pending rejection should be withdrawn.

Applicants hereby declare small entity status which should satisfy the Examiner's action.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims as amended should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 2/18/03



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Appendix 1

Version With Markings To Show Changes Made

In The Specification:

Please amend the paragraph beginning at Specification page 47, line 11 as follows:

"Figs. 1A-1H show [Fig. 1 is] a comparison of the nucleotide structure of the DNAP genes isolated from *Thermus aquaticus* (SEQ ID NO:1), *Thermus flavus* (SEQ ID NO:2) and *Thermus thermophilus* (SEQ ID NO:3); the consensus sequence (SEQ ID NO:7) is shown at the top of each row."

Please amend the paragraph beginning at Specification page 47, line 15 as follows:

"Figs. 2A-2C show [Fig. 2 is] a comparison of the amino acid sequence of the DNAP isolated from *Thermus aquaticus* (SEQ ID NO:4), *Thermus flavus* (SEQ ID NO:5), and *Thermus thermophilus* (SEQ ID NO:6); the consensus sequence (SEQ ID NO:8) is shown at the top of each row."

Please amend the paragraph beginning at Specification page 49, line 8 as follows:

"Figs. 22A and 22B demonstrate [Fig. 22 demonstrates] that the "nibbling" phenomenon is duplex dependent."

Please amend the paragraph beginning at Specification page 51, line 1 as follows:

"Figs. 42A and 42B provide images [Fig. 42 is the image] generated by a fluorescence imager showing the products of INVADER oligonucleotide-directed cleavage assays run using a HCV RNA target and demonstrate the stability of RNA targets under INVADER oligonucleotide-directed cleavage assay conditions."

Please amend the paragraph beginning at Specification page 52, line 14 as follows:

"Figures 59A-59E provide [Fig. 59 provides] an alignment of the amino acid sequences of several FEN-1 nucleases including the *Methanococcus jannaschii* FEN-1 protein

(MJAFEN1.PRO), the *Pyrococcus furiosus* FEN-1 protein (PFUFEN1.PRO), the human FEN-1 protein (HUMFEN1.PRO), the mouse FEN-1 protein (MUSFEN1.PRO), the *Saccharomyces cerevisiae* YKL510 protein (YST510.PRO), the *Saccharomyces cerevisiae* RAD2 protein (YSTRAD2.PRO), the *Shizosaccharomyces pombe* RAD13 protein (SPORAD13.PRO), the human XPG protein (HUMXPG.PRO), the mouse XPG protein (MUSXPG.PRO), the *Xenopus laevis* XPG protein (XENXPG.PRO) and the *C. elegans* RAD2 protein (CELRAD2.PRO) (SEQ ID NOS:135-145, respectively); portions of the amino acid sequence of some of these proteins were not shown in order to maximize the alignment between proteins (specifically, amino acids 122 to 765 of the YSTRAD2 sequence were deleted; amino acids 122 to 746 of the SPORAD13 sequence were deleted; amino acids 122 to 757 of the HUMXPG sequence were deleted; amino acids 122 to 770 of the MUSXPG sequence were deleted; and amino acids 122 to 790 of the XENXPG sequence were deleted). The numbers to the left of each line of sequence refers to the amino acid residue number; dashes represent gaps introduced to maximize alignment."

Please amend the paragraph beginning at Specification page 55, line 15 as follows:

"Figs. 88A and 88B provide schematics [Fig. 88 provides a schematic] illustrating that an uncut probe combined with a partial promoter oligonucleotide does not permit transcription while a cut probe combined with a partial promoter oligonucleotide generates a complete (but nicked) promoter which supports transcription."

Please amend the paragraph beginning at Specification page 56, line 23 as follows:

"Figs. 99A-99E depict [Fig. 99 depicts] structures that may be employed to determine the ability [ablity] of an enzyme to cleave a probe in the presence and the absence of an upstream oligonucleotide. Figs. 99A-99E display [Fig. 99 displays] the sequence of oligonucleotide 89-15-1 (SEQ ID NO:152), oligonucleotide 81-69-5 (SEQ ID NO:156), oligonucleotide 81-69-4 (SEQ ID NO155), oligonucleotide 81-69-3 (SEQ ID NO:154), oligonucleotide 81-69-2 (SEQ ID NO:153) and a portion of M13mp18 (SEQ ID NO:163)."

Please amend the paragraph beginning at Specification page 57, line 28 as follows:

"Figs. 107A-107C show [Fig. 107 shows] three images generated by a fluorescence imager showing that two different lengths of 2' O-methyl, 3' terminal amine-modified ARRESTOR oligonucleotide both reduce non-specific background cleavage of the secondary probe when included in the second step of a reaction where the cut probe from an initial invasive cleavage reaction is employed as an integrated INVADER-target complex in a second invasive cleavage reaction."

Appendix 2

1. A method for detecting a target sequence, comprising:
   a) providing:
      i) a sample suspected of containing said target sequence;
      ii) oligonucleotides capable of forming an invasive cleavage structure in the presence of said target sequence; and
      iii) an agent for detecting the presence of an invasive cleavage structure; and
   b) exposing said sample to said oligonucleotides and said agent under conditions such that said invasive cleavage structure is cleaved by said agent; and
   c) detecting the cleavage of said invasive cleavage structure.

2. The method of Claim 1, wherein said agent comprises a cleavage agent.

3. The method of Claim 2, wherein said exposing said sample to said oligonucleotides and said cleavage agent comprises exposing said sample to said oligonucleotides and said cleavage agent under conditions wherein an invasive cleavage structure is formed between said target sequence and said oligonucleotides if said target sequence is present in said sample, wherein said invasive cleavage structure is cleaved by said cleavage agent to form a cleavage product.

5. The method of Claim 1, wherein said target sequence comprises a first region and a second region, said second region downstream of and contiguous to said first region, and wherein said oligonucleotides comprise first and second oligonucleotides, said wherein at least a portion of said first oligonucleotide is completely complementary to said first region of said target sequence and wherein said second oligonucleotide comprises a 3' portion and a 5' portion, wherein said 5' portion is completely complementary to said second region of said target sequence.

6. The method of Claim 1, wherein said target sequence is selected from the group consisting of human cytomegalovirus viral DNA; polymorphisms in human apolipoprotein E gene; mutations in human hemochromatosis gene; mutations in human MTHFR; prothrombin 20210GA polymorphism; HR-2 mutation in human factor V gene; single nucleotide polymorphisms in human TNF-a gene, and Leiden mutation in human factor V gene.

7. A kit for detecting a target sequence comprising oligonucleotides capable of forming an invasive cleavage structure in the presence of said target sequence.

8. The kit of Claim 7, further comprising an agent for detecting the presence of an invasive cleavage structure.

9. The kit of Claim 8, wherein said agent comprises a cleavage agent.

10. (Amended) The kit of Claim 7, wherein said oligonucleotides comprise first and second oligonucleotides, said first oligonucleotide comprising a 5' portion complementary to a first region of said target sequence and said second oligonucleotide comprising a 3' portion and a 5' portion, said 5' portion complementary to a second region of said target sequence downstream of and contiguous to said first region of said target sequence.

11. The kit of Claim 7, wherein said target sequence is selected from the group consisting of human cytomegalovirus viral DNA; polymorphisms in human apolipoprotein E gene; mutations in human hemochromatosis gene; mutations in human MTHFR; prothrombin 20210GA polymorphism; HR-2 mutation in human factor V gene; single nucleotide polymorphisms in human TNF-a gene, and Leiden mutation in human factor V gene.

In The Claims:

Please cancel claim 4.

Please rewrite the following claims:

1. (Amended) A method for detecting a target sequence, comprising:
   a) providing:
      i) a sample suspected of containing said target sequence;
      ii) oligonucleotides capable of forming an invasive cleavage structure in the presence of said target sequence; and
      iii) an agent for detecting the presence of an invasive cleavage structure; and
   b) exposing said sample to said oligonucleotides and said agent[.] under conditions such that said invasive cleavage structure is cleaved by said agent; and
   c) detecting the cleavage of said invasive cleavage structure.

3. (Amended) The method of Claim 2, wherein said exposing said sample to said oligonucleotides and said cleavage agent comprises exposing said sample to said oligonucleotides and said cleavage agent under conditions wherein an invasive cleavage structure is formed between said target sequence and said oligonucleotides if said target sequence is present in said sample, wherein said invasive cleavage structure is cleaved by said cleavage agent to form a cleavage product.

5. (Amended) The method of Claim 1, wherein said target sequence comprises a first region and a second region, said second region downstream of and contiguous to said first region, and wherein said oligonucleotides comprise first and second oligonucleotides, said wherein at least a portion of said first oligonucleotide is completely complementary to said first region [portion] of said target sequence and wherein said second oligonucleotide comprises a 3' portion and a 5' portion, wherein

said 5' portion is completely complementary to said second region [portion] of said target sequence [nucleic acid].

10. (Amended) The kit of Claim 7, wherein said oligonucleotides comprise first and second oligonucleotides, said first oligonucleotide comprising a 5' portion complementary to a first region of said target sequence [nucleic acid] and said second oligonucleotide comprising a 3' portion and a 5' portion, said 5' portion complementary to a second region of said target sequence [nucleic acid] downstream of and contiguous to said first region [portion] of said target sequence [nucleic acid].